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Altered Excitation-Contraction Coupling in Heart Failure

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Introduction

An abnormal regulation of the intracellular Ca^{2+} by the sarcoplasmic reticulum (SR) is the chief pathogenic mechanism for various types of dysfunctions in heart failure. Thus, it becomes important to clarify the molecular mechanisms governing the highly regulated excitation-contraction coupling process and their alterations in heart failure in order to develop new therapeutic approaches for this disease. Recently, novel mechanism has been proposed with regard to the alterations in the excitation (E)-contraction (C) coupling process in heart failure. In this review, I focused on the role of FKBP12.6-mediated stabilization of Ca^{2+} release channel (ryanodine receptor: RyR) on the pathogenesis of intracellular Ca^{2+} overload seen in heart failure.

Intracellular Ca^{2+} transient as a key role in determining the mode of myocardial contraction

In myocardial contraction, Morgan's group [1] has shown the close relationship between the preceding Ca^{2+} transient and the following tension development. Also, in other paper using rat papillary muscle [2], the time to peak Ca^{2+} transient appeared to be clearly shortened as extracellular Ca^{2+} concentration increased, in association with an increase in the tension. On the basis of these findings, the acceleration rate as well as the deceleration rate of Ca^{2+} transient might greatly influence the following tension development.

Concerning the effect of calcium on the crossbridge cycle, once calcium is bound to troponin-C, a molecular signal is generated within the thin filament that eventually leads to an increased rate of crossbridge attachment with a form of positive cooperativity and hence leads to an increase in the rate of rise of tension .[3] These events for crossbridge cycling are considered to be occurring very rapidly from the beginning of the rise of Ca $^{2+}$ transient .[4] Therefore, it is likely that as cytosolic Ca^{2+} concentration elevates faster, the crossbridge attachment occurs faster, resulting in faster and/or higher tension development. Thus, the intracellular Ca^{2+} transient might play a key role in determining the mode of myocardial contraction.

Regulation of intracellular Ca^{2+} by sarcoplasmic reticulum

Major alterations in E-C coupling of heart failure have been characterized and related to contractile and relaxation functions. These dysfunctions are described by reduced twitch amplitude, delayed relaxation, and disturbed relaxation function, associated with parallel changes in intracellular whole Ca^{2+} transient.

In failing hearts, the duration of Ca^{2+} tran-

sient has been shown to be increased [5-6] although there is a controversy as to the change in the peak value of Ca^{2+} transient in heart failure. Perreault et al [5] demonstrated that there was no difference in the peak value of Ca^{2+} transient between normal and heart failure. In contrast, Yao et al[6] showed a significant reduction of peak Ca^{2+} transient between normal and heart failure. Since the major intracellular organ that regulates the intracellular Ca^{2+} transient is sarcoplasmic reticulum, its functional abnormality directly leads to the prolonged Ca^{2+} transient, hence resulting in contractile and relaxation dysfunctions. As a matter of fact, the abnormal regulation of intracellular Ca^{2+} by SR has been shown to be involved in the mechanism of contractile and relaxation dysfunction in heart failure. Several investigators have demonstrated that Ca^{2+} uptake by SR was decreased in association with the decreased density of Ca^{2+}-ATPase in cardiac hypertrophy and/or failure .[7-9]

The delayed fall of descending portion of Ca $^{2+}$ transient might be caused by the decrease in the expression and/or activity of the SR Ca $^{2+}$-ATPase (SERCA II) .[10] The decreased acceleration of Ca^{2+} transient (prolongation of time to peak Ca^{2+} transient) may be due mainly to the altered Ca^{2+} release function of the RyR because no other protein or receptor can induce faster Ca^{2+} release than the RyR.

In cardiac muscle, the majority of the Ca $^{2+}$ transient triggering contraction is provided by a large amount of Ca^{2+} release from SR following the small influx of Ca^{2+} through L-type Ca^{2+} channel, that is Ca^{2+}-induced Ca $^{2+}$ release .[11-12] The available Ca^{2+} for cardiac contraction is released from SR Ca^{2+} release channel, also referred to as ryanodine receptor (RyR).[13-14]

Using canine failing heart produced by rapid ventricular-pacing, Vatner et al [15] reported that the number of RyR was decreased even one day after rapid ventricular pacing in association with the decrease in LV contractility. In contrast, the number of RyR was increased in SR from prehypertrophic cardiomyopathic hamster heart .[16] We also demonstrated that the density of RyR was increased in mild pressure-overload rat hypertrophied heart [17], whereas it was decreased in volume-overloaded rat heart .[18] In a previous report [19], we also reported that the rate of Ca^{2+} release induced by RyR-specific Ca^{2+} release trigger, polylysine, was decreased in failing SR vesicles and that the polylysine concentration dependence of the initial rate of Ca^{2+} release and that of [^{3}H]ryanodine binding were shifted toward a lower concentration of polylysine in failing SR vesicles. This suggests that the channel gating function of the RyR is altered in heart failure. Thus, it has been suggested that the quantitative or qualitative alteration of RyR might affect the change in contractile function during the development of various types of cardiac hypertrophy and/or failure. With regard to the mechanism underlying the defective channel function of RyR, Gomez et al [20] proposed that a decrease in the functional coupling between DHP receptor and RyR might modulate Ca^{2+} release function of RyR. Recently, it has been demonstrated that the defectiveness of the channel gating function is also caused by the FKBP12.6-mediated stabilization of RyR.

Role of FKBP12.6-mediated stabilization of ryanodine receptor on Ca^{2+} release function

An associate protein, FKBP12 has been found to be co-purified with RyR during sucrose density gradient centrifugation .[21] The physiological function of FKBP12 is modulation of RyR-1, the skeletal muscle isoform of the Ca^{2+} release channel, possibly by enhancing cooperation among its four subunits .[21-23] Recently, a novel FKBP with a different electrophoretic mobility (FKBP12.6) was found to be specifically associated with RyR-2, the cardiac muscle isoform of the Ca $^{2+}$ release channel .[24-25] FKBP12.6 has 85 % homology with FKBP12 .[26] The stoichiometry of binding is approximately four moles of FKBP per RyR tetramer (or one FKBP to one RyR monomer) in both skeletal muscle and cardiac muscle.

Recently, we showed (i) that FK506 caused a dose-dependent Ca^{2+} leak in normal SR vesicles, (ii) that this leak showed a close parallelism with the conformational change in RyR and (iii) that the stoichiometry of FKBP with respect to RyR was significantly

decreased in failing SR vesicles, leading to an abnormal Ca^{2+} leak in heart failure .[27] (iv) the dramatic reduction in FKBP12.6 corresponds to the observation that application of the immunosuppressant agent FK506, to produce dissociation of FKBP12.6 from RYR in normal hearts, did not cause any further reduction in the rate of Ca^{2+} release from the SR vesicles isolated from failing hearts. This suggests that in heart failure the regulation of FKBP12.6 on RYR is absent, resulting in abnormal and maximal Ca^{2+} leak. Thus, the modification of the polylysine-induced SR Ca^{2+} release in heart failure is due to a reduced amount of FKBP 12.6. Namely, when a sufficiently high concentration of FK506 (or rapamycin) is applied to cardiac myocytes, cooperation among the four RyR subunits is disrupted, thus destabilizing the channel and in turn inducing an abnormality in the channel-gating function of RyR. In heart failure, because of the partial loss of FKBP12.6 from the RyR, equivalent phenomena are presumably occurring even in the absence of FKBP-dissociating agents. With regard to this, Marx et al. [28] have described a macromolecular complex in cardiac muscle formed by RYR2, FKBP12.6, protein kinase A (PKA), protein phospatases PP1 and PP2A and mAKAP (anchoring structure). The authors demonstrated that PKA hyperphosphorylation of RyR in failing hearts causes a dissociation of FKBP12.6 from RyR, resulting in the following abnormal single-channel properties: (i) increased Ca^{2+} sensitivity for activation and (ii) elevated channel activity associated with destabilization of the tetrameric channel complex. They proposed a model where, in normal hearts, a discrete phosphorylation of the complex due to β-stimulation could increase the Po of the channel and so increase the gain of E-C coupling (i.e. more Ca^{2+} release for the same cytoplasmic Ca^{2+} trigger). The hyperphosphorylated state of the failing myocardium would offset this regulation to its maximum so that β-stimulation would not produce any further increase in Po (blunt ? -stimulation response). The maximum RYR-FKBP 12.6 dissociation would also increase the Ca $^{2+}$ leak from the SR to produce a reduction in the SR Ca^{2+} content and increased diastolic $[Ca^{2+}]$. Taken together with these evidences, it could be concluded that the defectiveness of the mode of the FKBP12.6-mediated stabilization of RyR is the major cause of various abnormal functions in the failing heart.

In heart failure the delicate interactions between SR Ca^{2+} release complex molecules could transform a highly specialized regulatory mechanism into a structure "out of control". Recently, several evidences have accumulated concerning the disrupted relationship between FKBP12.6 and RYR in the pathogenesis of the development of heart failure. This new concept advances the understanding of the mechanism for contractile and relaxation dysfunction in heart failure, and also provides a valuable clue for the development of new methods of the treatment to prevent and cure heart failure

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